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EXAMINER	
FORMAN, BETTY J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,252	ELLINGTON, ANDREW	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12,15-25 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12,15-25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 23 January 2004 in which claims 1 and 15 were amended. The amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 27 October 2003, not reiterated below, are withdrawn in view of the amendments.

Applicant's arguments have been thoroughly reviewed and are discussed below as they apply to the instant rejections. New grounds for rejection, necessitated by amendment are discussed.

Claims 1, 6-12, 15-25 and 28 are under prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent

> or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 6-10, 12, 15, 19, 25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Pitner et al (U.S. Patent No. 5,691,145, issued 25 November 1997).

Regarding Claim 1, Pitner et al disclose a method of transducing a conformation change of a signaling aptamer (e.g. G-quartet, Column 2, lines 31-50) that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a reporter molecule (labeled nucleotide) that is coupled to the aptamer prior to binding (Column 5, lines 15-47), the method comprising, covalently coupling the reporter molecule to an aptamer to form a the signaling aptamer wherein the reporter replaces a nucleic acid within the aptamer (i.e. "interior..locations"; "near the ends, i.e. not linked to the terminal nucleotides"; and "within 2-4 nucleotides of the terminal nucleotide, Column 5, lines 16-17; 21-24; and 26-28), placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (Example 1, Column 7, lines 31-59).

Regarding Claim 6, Pitner et al disclose the method wherein the covalent coupling of the reporter molecule occurs during chemical synthesis (Column 5, lines 16-19).

Regarding Claims 7-9, Pitner et al disclose the method wherein the reported is a fluorescent dye i.e. fluorescein (Example 1 and Claim 7).

Regarding Claim 10, Pitner et al disclose the method wherein the aptamer is selected from RNA, DNA, modified RNA and modified DNA (Column 2, lines 31-50).

Regarding Claim 12, Pitner et al disclose the method wherein the ligand is in solution (Example 1, Column 7, lines 31-59).

Regarding Claim 15, Pitner et al disclose a method of transducing a conformation change of a signaling aptamer (e.g. G-quartet, Column 2, lines 31-50) that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a reporter molecule (labeled nucleotide) that is coupled to the aptamer prior to binding (Column 5, lines 15-47), the method comprising, covalently coupling a fluorescent dye to an aptamer to form a the signaling aptamer wherein the dye replaces a nucleic acid within the aptamer (i.e. "interior..locations"; "near the ends, i.e. not linked to the terminal nucleotides"; and "within 2-4 nucleotides of the terminal nucleotide, Column 5, lines 16-17; 21-24; and 26-28), placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (Example 1, Column 7, lines 31-59).

Regarding Claim 19, Pitner et al disclose the method wherein the fluorescent dye is fluorescein (Example 1 and Claim 7).

Regarding Claim 25, Pitner et al disclose the method wherein the ligand is in solution (Example 1, Column 7, lines 31-59).

Regarding Claim 28, Pitner et al disclose the method wherein the ligand is quantitated by correlating the increased fluorescence generated upon ligand binding to the unbound ligand signal (Column 9, lines 17-28).

4. Claims 1, 6-12, 15, 19, 23, 25 and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Jayasena et al (WO 99/31276, published 24 June 1999).

Regarding Claim 1, Jayasena et al disclose a method of transducing a conformation change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a reporter molecules that is appended to the aptamer prior to binding, the method comprising, covalently coupling the reporter molecule (fluorescein phosphoramidite, page 43, lines 12-27) to forma the signaling aptamer wherein the reporter replaces a nucleic acid in the aptamer, placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (page 32, line 14-page 34, line 30).

Regarding Claim 6, Jayasena et al disclose the method wherein the covalent coupling of the reporter molecule occurs during chemical synthesis (page 43, lines 12-27).

Regarding Claims 7-9, Jayasena et al disclose the method wherein the reported is a fluorescent dye i.e. fluorescein (page 43, lines 12-13).

Regarding Claim 10, Jayasena et al disclose the method wherein the aptamer is selected from RNA, DNA, modified RNA and modified DNA i.e. nucleic acid ligand (page 16, line 6-page 17, line 15).

Regarding Claim 11, Jayasena et al disclose the method wherein the ligand is not a nucleic acid sequence i.e. target (page 16, lines 21-26 and page 17, lines 16-22).

Regarding Claim 12, Jayasena et al disclose the method wherein the ligand is in solution (page 15, lines 8-11).

Regarding Claim 15, Jayasena et al disclose a method of transducing a conformation change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a fluorescent dye that is appended to the aptamer

prior to binding, the method comprising, covalently coupling the fluorescent dye (fluorescein phosphoramidite, page 43, lines 12-27) to forma the signaling aptamer wherein the dye replaces a nucleic acid in the aptamer, placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (page 32, line 14-page 34, line 30).

Regarding Claims 19, Jayasena et al disclose the method wherein the fluorescent dye is fluorescein (page 43, lines 12-13).

Regarding Claim 23, Jayasena et al disclose the method wherein the ligand is not a nucleic acid sequence i.e. target (page 16, lines 21-26 and page 17, lines 16-22).

Regarding Claim 25, Jayasena et al disclose the method wherein the ligand is in solution (page 15, lines 8-11).

Regarding Claim 28, Jayasena et al disclose the method wherein the ligand is quantitated by correlating the increased fluorescence generated upon ligand binding to the unbound ligand signal (page 30, lines 16-29).

Response to Arguments

5. As Applicant notes, Jayasena et al (WO 99/31276) is a continuation of the Jayasena patent and therefore contains the same teachings. As such, Applicant relies on the arguments discussed below regarding the Jayasena patent to traverse the above rejections. The arguments have been considered but are not found persuasive as detailed below.

6. Claims 1, 6-12, 15, 19, 23, 25 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Jayasena et al (U.S. Patent No. 6,531,286, filed 18 September 1998).

Regarding Claim 1, Jayasena et al disclose a method of transducing a conformation change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a reporter molecules that is appended to the aptamer prior to binding, the method comprising, covalently coupling the reporter molecule (fluorescein phosphoramidite, Column 29, lines 40-65) to form a the signaling aptamer wherein the reporter replaces a nucleic acid in the aptamer, placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (Column 23, lines 7-64 and Claim 1).

Furthermore, Jayasena et al teach the reporter molecule is coupled to the aptamer within the aptamer i.e. one or more positions "other than the 5' and 3' termini" (Column 19, lines 44-47) or "any locations in the ligand" (Column 19, lines 40-43).

Regarding Claim 6, Jayasena et al disclose the method wherein the covalent coupling of the reporter molecule occurs during chemical synthesis (Column 29, lines 40-65).

Regarding Claims 7-9, Jayasena et al disclose the method wherein the reported is a fluorescent dye i.e. fluorescein (Column 29, lines 40-65).

Regarding Claim 10, Jayasena et al disclose the method wherein the aptamer is selected from RNA, DNA, modified RNA and modified DNA i.e. nucleic acid ligand (Column 11, lines 10-51).

Regarding Claim 11, Jayasena et al disclose the method wherein the ligand is not a nucleic acid sequence i.e. target (Column 11, lines 33-41 and Column 12, lines 5-15).

Regarding Claim 12, Jayasena et al disclose the method wherein the ligand is in solution (Column 10, lines 35-41).

Regarding Claim 15, Jayasena et al disclose a method of transducing a conformation change of a signaling aptamer that occurs upon the signaling aptamer binding a ligand to a detectable increased signal generated by a fluorescent dye that is appended to the aptamer prior to binding, the method comprising, covalently coupling the fluorescent dye (fluorescein phosphoramidite, Column 29, lines 40-65) to form a the signaling aptamer wherein the dye replaces a nucleic acid in the aptamer, placing the signaling aptamer in solution, contacting the signaling aptamer in solution with the ligand under conditions whereby the aptamer binds the ligand and detecting the increase in fluorescence intensity generated by the reporter molecule transduced by conformational change in the signaling aptamer upon binding the ligand (Column 23, lines 7-64 and Claim 1).

Furthermore, Jayasena et al teach the fluorescent dye is coupled to the aptamer within the aptamer i.e. one or more positions "other than the 5' and 3' termini" (Column 19, lines 44-47) or "any locations in the ligand" (Column 19, lines 40-43).

Regarding Claims 19, Jayasena et al disclose the method wherein the fluorescent dye is fluorescein (Column 29, lines 40-65).

Regarding Claim 23, Jayasena et al disclose the method wherein the ligand is not a nucleic acid sequence i.e. target (Column 11, lines 33-41 and Column 12, lines 5-15).

Regarding Claim 25, Jayasena et al disclose the method wherein the ligand is in solution (Column 10, lines 35-41).

Regarding Claim 28, Jayasena et al disclose the method wherein the ligand is quantitated by correlating the increased fluorescence generated upon ligand binding to the unbound ligand signal (Column 20, lines 57-67).

Response to Arguments

7. Applicant asserts that the molecular beacon of Jayasena contains a loop structure that is complementary to a nucleic acid aptamer and therefore only binds to the aptamer, not the ligand as claimed. Applicant argues that the instantly claimed aptamer, in contrast to that of

Jayasena, comprises a reporter/dye molecule covalently attached therein wherein the reporter-linked aptamer binds to the ligand.

Regarding Jayasena, Applicant argues 1) the reporter molecule is not covalently coupled within the aptamer to form a signaling aptamer, but instead the reporter hybridizes to the aptamer; 2) the conformational change resulting from ligand binding does not "directly" transduce a change in fluorescence, but instead induces the molecular beacon to undergo a conformational change to transduce a change in fluorescence; and 3) the molecular beacon is a nucleic acid, not a signaling aptamer.

The arguments have been considered but are not found persuasive because the claims are drawn to a reporter molecule coupled to an aptamer thereby forming a signaling aptamer. The "molecular beacon" of Jayasena comprises a nucleic acid sequence covalently coupled to a reporter/dye molecule (Column 10, lines 10-24) wherein upon contacting a target molecule (ligand) the molecular beacon binds the target molecule (via hybridization to the nucleic acid ligand of Jayasena) to thereby cause a detectable increase in fluorescence (Column 10, lines 10-24). The claims require a signaling aptamer comprising an aptamer covalently coupled to a reporter/dye. The molecular beacon of Jayasena comprises an aptamer (stem-looped nucleic acid (Fig.2) covalently coupled to a reporter/dye within the aptamer (e.g. Column 19, lines 17-50). The claims further require contacting the signaling aptamer with a ligand and detecting fluorescence resulting from ligand-aptamer binding. Jayasena teaches contacting the signaling aptamer (molecular beacon) with a ligand (target) and detecting fluorescence resulting from ligand-aptamer binding via hybridization (Column 10, lines 10-24). The instant claim language "comprising" encompasses the binding via hybridization. In contrast to Applicant's assertion, the claims do not require "direct" binding of the ligand-aptamer. Hence, Jayasena teaches the method as claimed.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 20-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jayasena et al (U.S. Patent No. 6,531,286, filed 18 September 1998) in view of Szostak et al. (U.S. Patent No. 5,631,146, issued 20 May 1997)..

Regarding Claims 20-22 and 24, the claimed method embodiment differs from the method of Jayasena et al wherein the aptamer is an anti-adenosine RNA or DNA aptamer wherein the former is ATP-R-ACI3 and the latter is DFL7-8 and the ligand (target molecules) is adenosine. However, Jayasena et al note that numerous diagnostically important nucleic acid ligands that bind target molecules have been identified (Column 2, line 53-Column 4, line 64). Furthermore, the Szostak et al. patent teaches anti-adenosine triphosphate and anti-adenosine DNA aptamers prepared by the same process (Column 4, line 56-coIumn 6, line 9). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to employ an anti-adenosine aptamer in the method of Szostak et al in view of the Jayasena et al. teaching such aptamers (nucleic acid ligands) were known in the art and in view of the known benefit of employing an aptamer that was known and proven in the art and readily obtainable by synthesis of the published nucleotide sequence. It would have been obvious further to synthesize aptamer analogues of the claims 21 and 22 aptamers in view of the teaching of Szostak et al. of a large number of anti-adenosine aptamers having the same conserved region as the aptamer of claim 22 (Figure 4A) and the methods for producing them wherein such aptamers would have been

expected by one of ordinary skill in the art to function in the same manner as the aptamers of claims 21 and 22 in view of the reference teaching that the conserved regions are the critical adenosine binding regions (column 7, lines 29-35 and column 8, lines 47-52).

Response to Arguments

10. Applicant argues that Jayasena does not anticipate the inventions of Claims 1 and 15 and therefore, the teachings of Szostak cannot render the invention of Claims 20-22 and 24 obvious. The argument has been considered but is not found persuasive for the reasons stated above regarding Jayasena.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
March 25, 2004